ORIGINAL ARTICLE

Randomized Trial of Vaccines for Zaire Ebola Virus Disease

PREVAC Study Team*

ABSTRACT

BACKGROUND

Questions remain concerning the rapidity of immune responses and the durability and safety of vaccines used to prevent Zaire Ebola virus disease.

METHODS

We conducted two randomized, placebo-controlled trials — one involving adults and one involving children — to evaluate the safety and immune responses of three vaccine regimens against Zaire Ebola virus disease: Ad26.ZEBOV followed by MVA-BN-Filo 56 days later (the Ad26–MVA group), rVSVΔG-ZEBOV-GP followed by placebo 56 days later (the rVSV group), and rVSVΔG-ZEBOV-GP followed by rVSVΔG-ZEBOV-GP 56 days later (the rVSV–booster group). The primary end point was antibody response at 12 months, defined as having both a 12-month antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4.

RESULTS

A total of 1400 adults and 1401 children underwent randomization. Among both adults and children, the incidence of injection-site reactions and symptoms (e.g., feverishness and headache) was higher in the week after receipt of the primary and second or booster vaccinations than after receipt of placebo but not at later time points. These events were largely low-grade. At month 12, a total of 41% of adults (titer, 401 EU per milliliter) and 78% of children (titer, 828 EU per milliliter) had a response in the Ad26–MVA group; 76% (titer, 992 EU per milliliter) and 87% (titer, 1415 EU per milliliter), respectively, had a response in the rVSV group; 81% (titer, 1037 EU per milliliter) and 93% (titer, 1745 EU per milliliter), respectively, had a response in the rVSV–booster group; and 3% (titer, 93 EU per milliliter) and 4% (titer, 67 EU per milliliter), respectively, had a response in the placebo group (P<0.001 for all comparisons of vaccine with placebo). In both adults and children, antibody responses with vaccine differed from those with placebo beginning on day 14.

CONCLUSIONS

No safety concerns were identified in this trial. With all three vaccine regimens, immune responses were seen from day 14 through month 12. (Funded by the National Institutes of Health and others; PREVAC ClinicalTrials.gov number, NCT02876328; EudraCT numbers, 2017-001798-18 and 2017-001798-18/3rd; and Pan African Clinical Trials Registry number, PACTR201712002760250.)

The members of the writing committee (Mark Kieh, M.D., M.S.M.H.C., Laura Richert, M.D., Ph.D., Abdoul H. Beavogui, M.D., Ph.D., Birgit Grund, Ph.D., Bailah Leigh, M.D., Eric D'Ortenzio, M.D., Seydou Doumbia, M.D., Ph.D., Edouard Lhomme, M.D., Ph.D., Samba Sow, M.D., Renaud Vatrinet, Ph.D., Céline Roy, Ph.D., Stephen B. Kennedy, M.D., Sylvain Faye, Ph.D., Shelley Lees, Ph.D., Niouma P. Millimouno, M.D., Alseny M. Camara, M.D., Mohamed Samai, M.B., B.S., Ph.D., Gibrilla F. Deen, M.D., Moussa Doumbia, M.D., Hélène Espérou, M.D., Jerome Pierson, Ph.D., Deborah Watson-Jones, M.D., Ph.D., Alpha Diallo, M.D., M.P.H., Deborah Wentworth, M.P.H., Chelsea McLean, Ph.D., Jakub Simon, M.D., Aurélie Wiedemann, Ph.D., Bonnie Dighero-Kemp, B.Sc., Lisa Hensley, Ph.D., M.S.P.H., H. Clifford Lane, M.D., Yves Levy, M.D., Ph.D., Peter Piot, M.D., Ph.D., Brian Greenwood, M.D., Geneviève Chêne, M.D., Ph.D., James Neaton, Ph.D., and Yazdan Yazdanpanah, M.D., Ph.D.) assume responsibility for the overall content and integrity of this article.

Z AIRE EBOLA VIRUS DISEASE (EVD) OUT- breaks have high mortality and morbidity, place an enormous financial and logistic burden on public health systems of affected countries,[1,2] and can lead to worldwide disruption. The risk of reemergence of EVD is ever-present, as highlighted by the recurrences of EVD in the Democratic Republic of Congo and Guinea.[3,4]

Two vaccine strategies to prevent EVD — the recombinant vesicular stomatitis virus (rVSV)–based vaccine expressing the surface glycoprotein of *Zaire ebolavirus* (ZEBOV; the rVSVΔG-ZEBOV-GP vaccine) and the combination of an adenovirus type 26–vectored vaccine encoding the ZEBOV glycoprotein (Ad26.ZEBOV) followed by a booster dose of a modified vaccinia Ankara virus strain (MVA-BN-Filo)[5-15] — have received World Health Organization (WHO) prequalification status and were used during the most recent Ebola outbreaks. The rVSVΔG-ZEBOV-GP vaccine is designed as a one-dose vaccine and has been recommended for reactive ring vaccination use in persons at high risk for exposure during outbreaks; a ring strategy is used to identify contacts and contacts of contacts. The Ad26.ZEBOV–MVA-BN-Filo combination is a two-dose regimen, with the vaccines administered 56 days apart, that has recently been recommended for persons who are at some risk for EVD but are not considered to be at high risk.[16] We report here the results of two randomized, placebo-controlled trials, one involving adults and the other involving children, that were conducted under one protocol by the Partnership for Research on Ebola Vaccinations (PREVAC) consortium in western Africa to assess the safety of these vaccines, as well as the rapidity and durability of antibody responses to these vaccines.[17]

METHODS

TRIAL DESIGN AND PARTICIPANTS

The PREVAC protocol, which describes the design and methods of separate comparisons of the three vaccine regimens with placebo, separately in adults and children (two separate trials undertaken, conducted concurrently), has been published previously.[18] The protocol (version 4.0), statistical analysis plan, and descriptions of earlier versions of the protocol are provided with the full text of this article at NEJM.org.

Eligible adults 18 years of age or older and children 1 to 17 years of age, all without a history of EVD, who were not pregnant or breastfeeding, were enrolled at six sites in four West African countries. The full inclusion and exclusion criteria are provided in the protocol. Enrollment was staggered according to age group, starting with adults and with adolescents 12 to 17 years of age, followed by children 5 to 11 years of age, and finally children 1 to 4 years of age.

Participants were randomly assigned to receive the Ad26.ZEBOV vaccine (0.5 ml; 5×10^{10} viral particles), followed by the MVA-BN-Filo vaccine (0.5 ml; 1×10^8 infectious units) 56 days later (the Ad26–MVA group); the rVSVΔG-ZEBOV-GP vaccine (1.0 ml; 9.4×10^7 plaque-forming units), followed by placebo 56 days later (the rVSV group); the rVSVΔG-ZEBOV-GP vaccine, followed by a booster dose of the same vaccine 56 days later (the rVSV–booster group); or saline placebo. Two placebos were required in the trial owing to different fill volumes for the vaccines; the placebo groups were pooled for analysis (Section S3.1 in the Supplementary Appendix, available at NEJM.org).[18]

An independent data and safety monitoring committee provided trial oversight. The trial protocol was approved by the Food and Drug Administration and by ethics committees of the sponsors.

The authors vouch for the accuracy and completeness of the analyses and data reported. Representatives of Merck Sharp and Dohme and Janssen (which provided the vaccines) and of the funding organizations participated in the preparation of the protocol and of the manuscript.

FOLLOW-UP

Follow-up visits occurred on days 7, 14, and 28 after the first dose of vaccine or placebo. The second or booster dose of vaccine or placebo was administered on day 56, with further follow-up visits at day 63 and during months 3, 6, and 12. Antibody response was assessed at each follow-up visit, injection-site reactions and symptoms (e.g., feverishness and headache) were assessed through month 6, and data on serious adverse events were collected through month 12.

ANTIBODY RESPONSES TO EBOLA GLYCOPROTEIN

Serum concentrations of IgG binding antibodies against the Ebola virus surface glycoprotein were measured at baseline and at each follow-

up visit with the Filovirus Animal Nonclinical Group (FANG) enzyme-linked immunosorbent assay (ELISA) (Section S3.6.1 and the protocol). The primary immunogenicity end point was an antibody response at month 12, with response defined as an antibody concentration of at least 200 ELISA units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. As in other studies, including the Partnership for Research on Ebola Virus in Liberia (PREVAIL) I trial,[9] an increase from baseline in the antibody concentration by at least a factor of 4 was used to define antibody response. An antibody concentration of at least 200 EU per milliliter and an increase from baseline by at least a factor of 2 were included because it was considered a possible correlate of protection.[19] As a secondary objective, we compared the rVSVΔG-ZEBOV-GP and Ad26.ZEBOV–MVA-BN-Filo regimens, separately, with placebo in an analysis of immediacy of response at day 14.

The protocol also specified primary objectives in support of regulatory submissions by Merck Sharp and Dohme and Janssen. These objectives stated that the time point of the antibody comparison with placebo for the rVSVΔG-ZEBOV-GP vaccine (Merck Sharp and Dohme) would be day 28 and the time point for the Ad26.ZEBOV–MVA-BN-Filo regimen (Janssen) would be month 3.

Antibody concentrations were determined in two laboratories: the Liberian Institute for Biomedical Research in Charlesville, Liberia, and the National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility in Frederick, Maryland. Specimens that were obtained from participants who had undergone randomization in Guinea and Sierra Leone were analyzed at the Liberian Institute for Biomedical Research laboratory, and those from participants who had undergone randomization in Liberia and Mali were analyzed at the NIAID Integrated Research Facility.

STATISTICAL ANALYSIS

Sample sizes for comparing each vaccine regimen with placebo with regard to antibody response and serious adverse events, separately among adults and children, exceeded those required. A larger-than-required sample size was specified because if a correlate of protection was identified after the start of the trial, the plan was to compare the active vaccines with one another (Sections S3.2 and S4). For the comparisons before the second injection in the rVSV group (which was placebo) and the rVSV–booster group, data from the two groups were pooled.

Data from adults and children were analyzed as two separate trials, with the use of identical statistical analyses. The trial involving children also included additional, prespecified analyses (see below).

Each active vaccine was compared with the pooled placebo group in the analysis of antibody response at month 12 with the use of logistic regression with trial site as a covariate. Odds ratios with 95% confidence intervals were used to compare percentages of participants with an antibody response between each vaccine regimen and placebo at each follow-up visit. Additional analyses to further characterize the antibody response are described in the Supplementary Appendix.

After log_{10} transformation, the mean antibody concentrations were compared between the vaccine groups and the placebo group at each follow-up visit, with the use of analysis of covariance with the baseline log_{10} level and site as covariates. Geometric mean concentrations after back-transformation are reported. Geometric mean ratios (for each vaccine vs. placebo) and 95% confidence intervals are also reported.

Subgroup analyses for antibody response were performed according to laboratory and according to country within laboratory. In addition, in the trial involving children, we performed prespecified subgroup analyses according to age group.

For each of the two trials, one involving children and one involving adults, we used a two-sided significance level of 0.0167 (Bonferroni method) to control the type I error for the three comparisons of each vaccine group with the placebo group for the primary analysis at month 12. Because the statistical analysis plan did not include a provision for correcting for multiplicity across outcomes, results for secondary outcomes are reported as point estimates with 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

From April through December 2018, a total of 1400 adults and 1401 children were enrolled in the two trials (Figs. S1 and S2). The characteristics of the participants in the randomized groups were balanced at baseline (Table 1).

In the trial involving adults, the median age was 27 years (interquartile range, 20 to 38), and 45% of the participants were women. At baseline, 15% of the adults had an antibody concentration of at least 200 EU per milliliter. The percentage of participants with an antibody concentration of at least 200 EU per milliliter at baseline was higher in Guinea (13%), Liberia (21%), and Sierra Leone (21%) than in Mali (5%) (Table S1).

In the trial involving children, one third of the participants were enrolled in each of the three age groups: 1 to 4 years, 5 to 11 years, and 12 to 17 years; 46% of the children were female. At baseline, 12% of the children had an antibody concentration of at least 200 EU per milliliter. As was observed with the adults, among children 12 to 17 years and 5 to 11 years of age, the percentage of participants with an antibody concentration of at least 200 EU per milliliter was lower in Mali than other countries; this relationship was not seen among participants 1 to 4 years of age.

ADHERENCE TO BOOSTER VACCINATION AND COMPLETENESS OF PRIMARY ANTIBODY OUTCOME

The second injection was administered to 92 to 96% of the adults and to 97 to 99% of the children (Table S2). The primary end point was assessed in more than 90% of the adults and children (Table S3).

SAFETY

Injection-Site Reactions and Symptoms in Adults

Most injection-site reactions and symptoms were reported by participants in the 7 days after vaccination, were more frequent in the active-vaccine groups than in the placebo group, and were largely of grade 1 severity (Table 2 and Table S4). Through day 7, the incidence of injection-site reaction was 9% in the Ad26–MVA group, 22% in the pooled rVSV groups, and 5% in the placebo group. The percentages of participants who reported symptoms through day 7 were 50%, 66%, and 44%, respectively. By day 14, the frequency of injection-site reactions and symptoms were similar in the Ad26–MVA group, the pooled rVSV groups, and the placebo group (Table 2). Similar trends were observed after the second or booster vaccinations (Table 2 and Table S5). By month 3, the percentage of participants reporting injection-site reactions and symptoms was similar in the vaccine groups and the placebo group (Table 2).

Serious Adverse Events and Deaths through 12 Months in Adults

Serious adverse events were reported in 14 of 396 adults (4%) in the Ad26–MVA group, 6 of 395 (2%) in the rVSV group, 1 of 197 (1%) in the rVSV–booster group, and 5 of 412 (1%) in the pooled placebo group (Table 2 and Table S6). Overall, 6 adults died: 2 in the Ad26–MVA group (from septic shock and myocardial infarction, in 1 participant each), 3 in the rVSV group (from sepsis, HIV infection, and appendicitis, in 1 each), and 1 in the placebo group (from malaria). None of the deaths were judged by the site investigator to be related to the vaccine or placebo.

Injection-Site Reactions and Symptoms in Children

As in adults, most injection-site reactions and symptoms that were reported in children occurred in the week after the first injection (through day 7), were more frequent in the vaccine groups than in the placebo group, and were largely of grade 1 severity (Table 2 and Table S7). Through day 7, the incidence of injection-site reaction was 15% in the Ad26–MVA group, 21% in the pooled rVSV groups, and 5% in the placebo group. Symptoms through day 7 were reported in 48%, 60%, and 43% of the participants, respectively. Through day 14, the incidences of injection-site reactions and symptoms were similar in the Ad26–MVA group, the pooled rVSV groups, and the placebo group. Similar trends were observed after the second injection (Table 2 and Table S8). By month 3, the incidence of symptoms was similar in the vaccine groups and the placebo group. Differences between the vaccine groups and the placebo group were similar in each age group (Tables S9 through S13).

Serious Adverse Events and Deaths through 12 Months in Children

Serious adverse events were reported in 5 of 403 children (1%) in the Ad26–MVA group, in 9 of 407 (2%) in the rVSV group, in 3 of 202 (1%) in

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Ad26–MVA Group	rVSV Group	rVSV–Booster Group	Placebo Group	Total
Adults					
No. of participants	396	395	197	412	1400
Age					
Median (IQR) — yr	27 (21–40)	27 (20–39)	26 (20–35)	27 (20–38)	27 (20–38)
Distribution — no. (%)					
18–29 yr	227 (57)	213 (54)	119 (60)	238 (58)	797 (57)
30–39 yr	67 (17)	89 (23)	41 (21)	84 (20)	281 (20)
≥40 yr	102 (26)	93 (24)	37 (19)	90 (22)	322 (23)
Female sex — no. (%)	171 (43)	182 (46)	87 (44)	187 (45)	627 (45)
Country — no. (%)					
Guinea	121 (31)	130 (33)	66 (34)	135 (33)	452 (32)
Liberia	73 (18)	70 (18)	35 (18)	81 (20)	259 (18)
Mali	81 (20)	84 (21)	41 (21)	86 (21)	292 (21)
Sierra Leone	121 (31)	111 (28)	55 (28)	110 (27)	397 (28)
HIV-positive status — no. (%)	6 (2)	13 (3)	2 (1)	4 (1)	25 (2)
Ebola IgG concentration†					
≥200 EU/ml — no./total no. (%)	50/394 (13)	58/388 (15)	32/197 (16)	68/409 (17)	208/1388 (15)
<66.96 EU/ml — no./total no. (%)	142/394 (36)	144/388 (37)	66/197 (34)	146/409 (36)	498/1388 (36)
Median (IQR) — EU/ml	94 (43–149)	92 (45–145)	94 (46–143)	96 (47–156)	95 (46–148)
Geometric mean — EU/ml	85	87	91	90	88
Children					
No. of participants	403	407	202	389	1401
Age					
Median (IQR) — yr	8 (4–13)	9 (4–12)	8 (3–13)	8 (4–13)	8 (4–13)
Distribution — no. (%)					
1–4 yr	137 (34)	123 (30)	71 (35)	136 (35)	467 (33)
5–11 yr	127 (32)	146 (36)	65 (32)	129 (33)	467 (33)
12–17 yr	139 (34)	138 (34)	66 (33)	124 (32)	467 (33)
Female sex — no. (%)	186 (46)	185 (45)	85 (42)	182 (47)	638 (46)
Country — no. (%)					
Guinea	163 (40)	156 (38)	77 (38)	150 (39)	546 (39)
Liberia	64 (16)	66 (16)	33 (16)	55 (14)	218 (16)
Mali	95 (24)	94 (23)	46 (23)	91 (23)	326 (23)
Sierra Leone	81 (20)	91 (22)	46 (23)	93 (24)	311 (22)
Ebola IgG concentration†					
≥200 EU/ml — no./total no. (%)	43/398 (11)	47/401 (12)	19/200 (10)	54/386 (14)	163/1385 (12)
<66.96 EU/ml — no./total no. (%)	198/398 (50)	187/401 (47)	97/200 (48)	188/386 (49)	670/1385 (48)
Median (IQR) — EU/ml	67 (29–127)	74 (33–122)	69 (33–122)	71 (33–141)	70 (32–128)
Geometric mean — EU/ml	63	67	67	70	66

* Two randomized, placebo-controlled trials — one involving adults and one involving children — evaluated the safety and immune responses of three vaccine regimens against Ebola virus disease: the Ad26.ZEBOV vaccine followed by the MVA-BN-Filo vaccine 56 days later (the Ad26–MVA group), the rVSVΔG-ZEBOV-GP vaccine followed by placebo 56 days later (the rVSV group), and the rVSVΔG-ZEBOV-GP vaccine followed by a booster dose of the same vaccine 56 days later (the rVSV–booster group). Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and IQR interquartile range.

† An Ebola IgG concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter was considered to indicate positivity. The assay developer's lower limit of quantification was 66.96 EU per milliliter. The median concentration and geometric mean concentration were assessed among participants with a result.

Table 2. Injection-Site Reactions, Targeted Symptoms, and Serious Adverse Events.*

Event	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
	number of participants with event/total number (percent)				
Adults					
Injection-site reaction after first injection					
At 0–7 days	36/396 (9)†	133/592 (22)‡	—	—	21/412 (5)
At 14 days	2/387 (1)	1/579 (<1)	—	—	0/404
Symptoms after first injection					
At 0–7 days	198/396 (50)	390/592 (66)‡	—	—	182/412 (44)
At 14 days	92/387 (24)	133/579 (23)	—	—	100/404 (25)
Injection-site reaction after second injection					
At 56–63 days	49/380 (13)‡	—	12/365 (3)	20/187 (11)†	20/392 (5)
At 3 mo	0/369	—	1/356 (<1)	1/187 (1)	0/385
Symptoms after second injection					
At 56–63 days	124/382 (32)	—	127/373 (34)	76/188 (40)	127/398 (32)
At 3 mo	122/373 (33)	—	95/371 (26)	53/188 (28)	102/393 (26)
Serious adverse event or death§	14/396 (4)	—	6/395 (2)	1/197 (1)	5/412 (1)
Death	2/396 (1)	—	3/395 (1)	0/197	1/412 (<1)
Children					
Injection-site reaction after first injection					
At 0–7 days	59/403 (15)‡	126/609 (21)‡	—	—	19/389 (5)
At 14 days	1/397 (<1)	1/603 (<1)	—	—	0/380
Symptoms after first injection					
At 0–7 days	195/403 (48)	363/609 (60)‡	—	—	166/389 (43)
At 14 days	64/397 (16)	93/603 (15)	—	—	70/380 (18)
Injection-site reaction after second injection					
At 56–63 days	55/398 (14)‡	—	26/396 (7)	23/198 (12)‡	16/381 (4)
At 3 mo	0/392	—	0/392	0/197	0/378
Symptoms after second injection					
At 56–63 days	127/399 (32)	—	112/400 (28)	64/198 (32)	106/383 (28)
At 3 mo	85/393 (22)	—	93/396 (23)	41/198 (21)	90/380 (24)
Serious adverse event or death¶	5/403 (1)	—	9/407 (2)	3/202 (1)	8/389 (2)
Death	0/403	—	3/407 (1)	0/202	2/389 (1)

* Data for the rVSV group and the rVSV–booster group were pooled for the assessment after receipt of the primary dose because all the participants in these groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine. The second injection was administered on day 56. Targeted symptoms included feverishness and headache. Serious adverse events and deaths were assessed in adults and children through month 12.
† P=0.016 for the comparison of vaccine with placebo, which was below the P-value threshold of less than 0.0167.
‡ P<0.001 for the comparison of vaccine with placebo.
§ Of the 26 adults with a serious adverse event, 12 events were attributed to appendicitis, all in women. There was no evidence of a difference in the incidence of appendicitis between the vaccine groups and the placebo group.
¶ Four of the serious adverse events in children were attributed to appendicitis.

the rVSV–booster group, and in 8 of 389 (2%) in the placebo group (Table 2 and Table S14). Overall, 5 children died: 3 children in the rVSV group (from sudden unexplained death, drowning, and fever of unknown origin, in 1 participant each) and 2 in the placebo group (from cardiopulmonary failure after malaria and from suspected meningitis, in 1 participant each). None of the deaths were judged by the site investigator to be related to the vaccine or placebo.

ANTIBODY RESPONSES

Among adults at month 12, the percentages of participants with an antibody response and the geometric mean concentrations were 41% and 401 EU per milliliter in the Ad26–MVA group, 76% and 992 EU per milliliter in the rVSV group, 81% and 1037 EU per milliliter in the rVSV–booster group, and 3% and 93 EU per milliliter in the placebo group (P<0.001 for all comparisons of vaccine with placebo) (Table 3). In both the Ad26–MVA and rVSV–booster groups, the percentages of participants with an antibody response and the geometric mean concentrations were greatest 7 days after receipt of the second or booster vaccination (day 63) and at month 3. By month 12, the percentage of participants with a response and the geometric mean concentrations had decreased to the levels that had been observed before the receipt of the second or booster vaccination (Table 3 and Fig. 1A).

Among children at month 12, the percentages of participants with a response and the geometric mean concentrations were 78% and 828 EU per milliliter in the Ad26–MVA group, 87% and 1415 EU per milliliter in the rVSV group, 93% and 1745 EU per milliliter in the rVSV–booster group, and 4% and 67 EU per milliliter in the placebo group (P<0.001 for all comparisons of vaccine with placebo) (Table 3 and Tables S17 and S18). In each of the vaccine groups, the percentages of participants with a response and the geometric mean concentrations at month 12 were greater among children than among adults. Among children, as was observed among adults, both the Ad26–MVA and rVSV–booster groups had their greatest percentage of participants with a response and highest geometric mean concentrations at visits shortly after the second or booster vaccination (day 63) and at month 3. By month 12, the percentage of

participants with a response and the geometric mean concentrations had decreased to the levels observed immediately before the receipt of the second or booster vaccination (Table 3 and Fig. 1B).

These results were similar in an analysis that excluded participants with a baseline (prevaccination) antibody concentration of at least 200 EU per milliliter, since these persons may have had an asymptomatic infection in a previous outbreak (Table S19). Results were also similar to those in the primary analysis when we imputed the assay developer's lower limit of quantification (66.96 EU per milliliter) for baseline and follow-up antibody concentrations below that level (Table S20). To facilitate consideration in the context of previous studies, we determined antibody responses for a range of differences in the factor increase (Table 4) and follow-up antibody levels above a specific level (Tables S21 and S22).

Subgroup analyses according to laboratory and country are provided in the Figures S3 through S8 and Tables S23 and S24. Although there were differences in the geometric mean concentrations among the countries and laboratories, all the differences in response between the vaccine group and the placebo group were large and followed a similar pattern of geometric mean concentrations over follow-up among both the adults and children, regardless of country or laboratory.

DISCUSSION

These two trials provide immunogenicity and safety data for three Zaire Ebola vaccine regimens in adults and in children 1 year of age or older. By day 14 after the first injection, an antibody response was observed with both vaccines (i.e., Ad26.ZEBOV and rVSV). The peak percentage of participants with a response in each group was observed at month 3 (28 days after the receipt of the second dose) in the Ad26–MVA group among both adults and children, at day 28 in the rVSV group among both adults and children, and at day 63 among adults and at month 3 among children in the rVSV–booster group.

There is no universally agreed-on correlate of protective immunity to EVD, and in this trial we were unable to assess protection from disease given that there were no incident cases of EVD.

Table 3. Geometric Mean Concentrations and Antibody Response According to Follow-up Visit.*

Variable	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
Adults					
At 7 days					
No. of participants	379	560	—	—	396
Geometric mean concentration (EU/ml)	87	91	—	—	79
Percentage of participants with response	2	2	—	—	1
At 14 days					
No. of participants	375	561	—	—	386
Geometric mean concentration (EU/ml)	244	428	—	—	89
Percentage of participants with response	22	44	—	—	1
At 28 days					
No. of participants	374	553	—	—	381
Geometric mean concentration (EU/ml)	355	1218	—	—	87
Percentage of participants with response	36	80	—	—	1
At 56 days					
No. of participants	369	541	—	—	364
Geometric mean concentration (EU/ml)	387	1193	—	—	96
Percentage of participants with response	41	84	—	—	2
At 63 days					
No. of participants	362	—	355	182	354
Geometric mean concentration (EU/ml)	2726	—	1243	4819	96
Percentage of participants with response	82	—	85	98	2
At 3 mo					
No. of participants	359	—	360	184	360
Geometric mean concentration (EU/ml)	3328	—	1084	3294	91
Percentage of participants with response	94	—	81	96	2
At 6 mo					
No. of participants	365	—	368	184	359
Geometric mean concentration (EU/ml)	666	—	973	1221	103
Percentage of participants with response	69	—	80	87	4
At 12 mo					
No. of participants	374	—	371	185	377
Geometric mean concentration (EU/ml)	401	—	992	1037	93
Percentage of participants with response†	41	—	76	81	3
Children					
At 7 days					
No. of participants	379	571	—	—	365
Geometric mean concentration (EU/ml)	74	69	—	—	61
Percentage of participants with response	2	1	—	—	1
At 14 days					
No. of participants	382	586	—	—	372
Geometric mean concentration (EU/ml)	377	440	—	—	64
Percentage of participants with response	48	58	—	—	1

Table 3. (Continued.)

Variable	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
At 28 days					
No. of participants	389	580	—	—	369
Geometric mean concentration (EU/ml)	572	1688	—	—	62
Percentage of participants with response	66	90	—	—	1
At 56 days					
No. of participants	389	584	—	—	362
Geometric mean concentration (EU/ml)	679	1561	—	—	68
Percentage of participants with response	73	91	—	—	2
At 63 days					
No. of participants	382	—	392	186	356
Geometric mean concentration (EU/ml)	10,605	—	1560	9750	69
Percentage of participants with response	97	—	92	99	3
At 3 mo					
No. of participants	380	—	388	194	362
Geometric mean concentration (EU/ml)	9406	—	1351	5103	63
Percentage of participants with response	98	—	90	99	1
At 6 mo					
No. of participants	381	—	388	191	344
Geometric mean concentration (EU/ml)	1254	—	1153	1963	66
Percentage of participants with response	88	—	86	95	4
At 12 mo					
No. of participants	381	—	385	189	364
Geometric mean concentration (EU/ml)	828	—	1415	1745	67
Percentage of participants with response†	78	—	87	93	4

* The geometric mean concentration was based on a $\log_{10}$ concentration with baseline $\log_{10}$ titer and trial site as covariates. A response was defined as an antibody concentration of at least 200 EU per milliliter and an increase from baseline in the antibody concentration by a factor of at least 4. The 95% confidence intervals for the geometric mean ratios and odds ratios for the comparisons of vaccine groups with the placebo group are provided in Tables S15 and S16. Data for the rVSV group and the rVSV–booster group are pooled up to the day 56 assessment because until that time point, participants in both groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine.
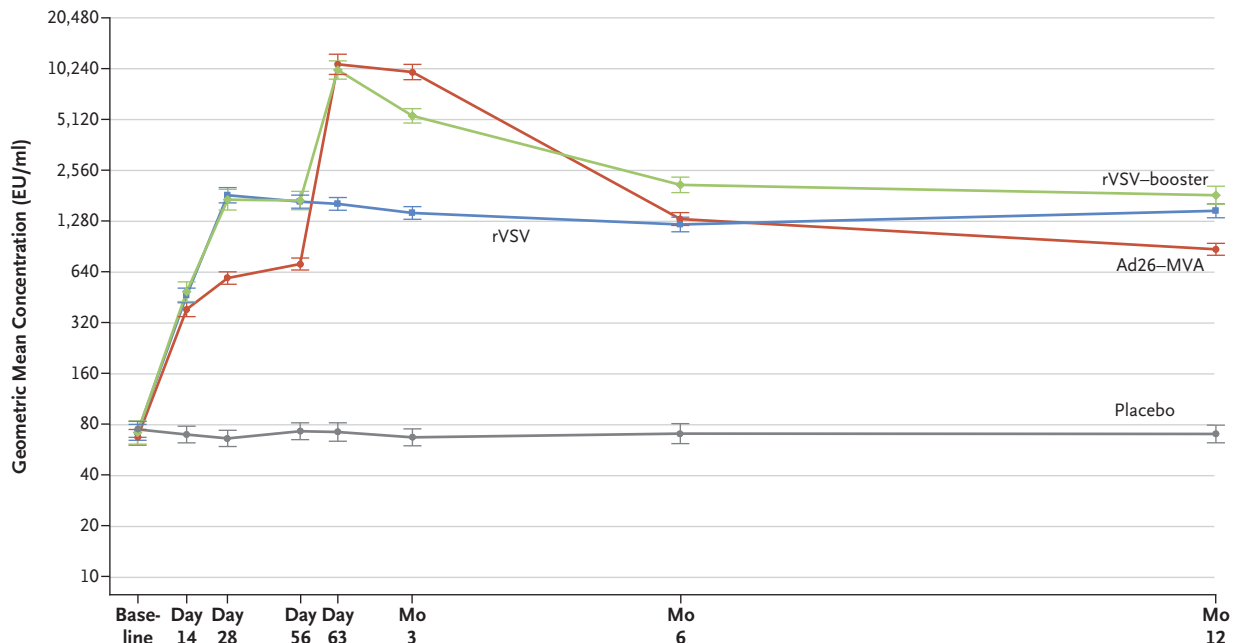
† P<0.001 for the comparison of each vaccine group with the placebo group at month 12.

However, it has been shown that levels of glycoprotein-binding antibodies strongly correlate with neutralizing antibody titers in nonhuman primates and humans.[20-22] Moreover, the use of results from a clinical trial of a single dose of rVSVΔG-ZEBOV-GP, the threshold of 200 EU per milliliter, and an increase from baseline in the antibody concentration by a factor of 2 or more seem to be a reasonable correlate of protection for that vaccine.[19] Consequently, an analysis that is based on immunogenicity data such as the one reported here is useful in the evaluation of vaccination strategies against EVD.

Geometric mean concentrations of antibodies to the Ebola surface glycoprotein were above the threshold of 200 EU per milliliter for at least 12 months in the majority of participants.[19] One of the challenges in this field of study is that considerable variability exists in the measurements of antibody levels. As described in the Supplementary Appendix, variability in the results was seen over time and as a function of test laboratory. However, the findings that pooled the results across laboratory and country were qualitatively similar to those for each laboratory and country considered separately.

A Adults

Geometric Mean Concentration (EU/ml)

rVSV–booster

rVSV

Ad26–MVA

Placebo

Base-line | Day 14 | Day 28 | Day 56 | Day 63 | Mo 3 | Mo 6 | Mo 12

No. of Participants
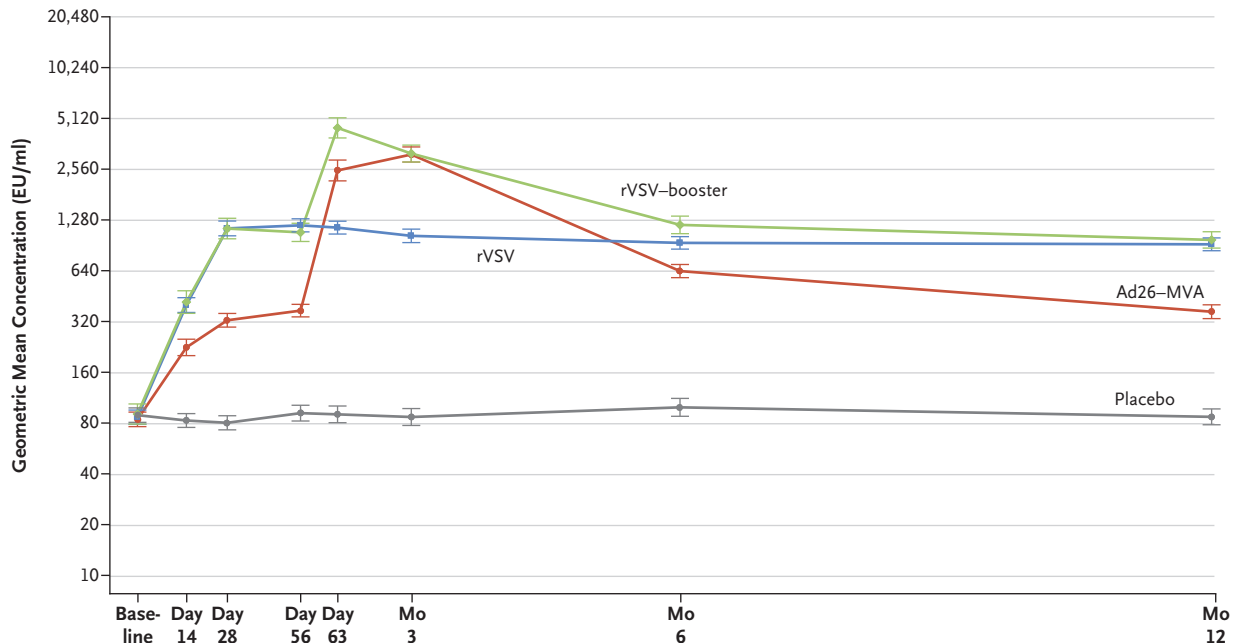
	Base-line	Day 14	Day 28	Day 56	Day 63	Mo 3	Mo 6	Mo 12
rVSV–booster	197	187	188	184	182	184	184	185
rVSV	388	381	372	364	361	367	375	378
Ad26–MVA	394	377	376	371	364	361	367	376
Placebo	409	388	384	366	356	363	361	379

B Children

Geometric Mean Concentration (EU/ml)

rVSV–booster

rVSV

Ad26–MVA

Placebo

Base-line | Day 14 | Day 28 | Day 56 | Day 63 | Mo 3 | Mo 6 | Mo 12

No. of Participants

	Base-line	Day 14	Day 28	Day 56	Day 63	Mo 3	Mo 6	Mo 12
rVSV–booster	200	195	191	195	188	196	193	191
rVSV	401	398	396	397	398	393	392	391
Ad26–MVA	398	386	393	394	386	384	386	386
Placebo	386	374	372	364	359	364	346	367

Figure 1 (facing page). Antibody Response in Adults and Children (Geometric Mean Concentrations), According to Trial Visit.

The geometric mean concentration was based on a $\log_{10}$ concentration with baseline $\log_{10}$ titer and trial site as covariates. Antibody response was defined as an antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. Geometric mean concentrations are shown. I bars indicate 95% confidence intervals.

Given that vaccines against EVD have typically been administered during an outbreak to populations at risk for infection, it was important to investigate the early kinetics of the antibody response. In this regard, both the rVSVΔG-ZEBOV-GP and Ad26.ZEBOV vaccinations led to an increase in geometric mean antibody concentrations beginning at day 14.

The use of primary immunization followed by booster immunization is standard practice for several vaccines. Data on rVSV booster immunizations for Ebola are limited. In this trial, the effect of a second injection of rVSVΔG-ZEBOV-GP at 56 days provided only a transient increase in antibody concentrations, a finding that is in line with responses that have been observed with other live-attenuated vaccines.[23] Additional trials (e.g., ClinicalTrials.gov number, NCT02788227) are under way to determine the effect of a booster given at a later time.

We observed higher antibody concentrations with the Ad26–MVA and rVSV vaccines in children than we did in adults. These data are consistent with findings from studies with a variety of different vaccines, including Ad26.ZEBOV–MVA-BN-Filo and rVSVΔG-ZEBOV-GP,[13,14,24] and probably reflect the more complete immunologic repertoire in children than in adults.[25] Differences in response may also be observed on the basis of host genetic and environmental factors. It has also been shown that the kinetic features of antibodies in children who are vaccinated with rVSVΔG-ZEBOV-GP may differ from those in adults.[24]

No safety concerns were identified in either the adults or children. Side effects were generally mild to moderate in intensity, were time-limited, and were similar to those in previous studies.[11,13,14,20,24,26] Our results regarding the safety of these vaccines have implications for the use of Ebola vaccines in children. Although the Ad26–MVA regimen has received marketing authorization for persons 1 year of age or older from the European Medicines Agency, the licensing of the rVSVΔG-ZEBOV-GP vaccine has thus far been limited to adults.

The PREVAC protocol and our trial findings have several strengths. First, sample sizes were determined to provide reasonable power to analyze antibody and safety results in both adults and children. Second, good follow-up rates were achieved by means of continuous community engagement and ongoing trust building throughout the clinical trial process. Third, we evaluated the two EVD vaccines that have been recommended by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) as compared with a common placebo group, separately in adults and children. Finally, this research was conducted through an international consortium that includes research and academic institutions from the United States, Europe, and western Africa with strong collaborative partnerships.

These two trials have some limitations. We were unable to assess protection from disease or determine a correlate of protection. Although the FANG ELISA, conducted by the Liberian Institute for Biomedical Research and the NIAID Integrated Research Facility, was performed with standard quality controls and has been used to measure antibody responses to the Ebola surface glycoprotein in a previous trial in Liberia,[9] it has not been validated for regulatory submissions. As described in the Supplementary Appendix, variability in the measurements of antibody levels to Ebola virus surface glycoprotein was seen both over time and between the two laboratories. Immunologic correlates of protection have not been established for Ebola vaccines in humans; thus, it is not possible to compare the degree of protection provided by each vaccine because the vaccines generate immune responses by means of different platforms and potentially different mechanisms. Although it has been shown that glycoprotein-specific binding antibodies strongly correlate with neutralizing antibody titers in nonhuman primates and in humans,[9,20-22] any potential binding antibody threshold above which humans would have a high probability of protection is unknown.

Data from these two trials add to evidence on immunogenicity and safety of the Ad26.ZEBOV–MVA-BN-Filo combination and the rVSVΔG-ZEBOV-GP vaccine against EVD in adults and children.

Table 4. Distribution of Increase in Antibody Concentration from Baseline.*

Variable	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
Adults					
Response at 28 days					
No. of participants	374	553	365	188	381
Factor increase — % of participants (cumulative %)				—	
≥8.0×	22 (22)	60 (60)	—	—	1 (1)
4.0–7.9×	14 (36)	20 (80)	—	—	<1 (1)
3.0–3.9×	6 (42)	6 (87)	—	—	<1 (1)
2.5–2.9×	6 (49)	3 (90)	—	—	0 (1)
2.0–2.4×	5 (54)	3 (93)	—	—	<1 (2)
1.0–1.9×	12 (66)	4 (97)	—	—	5 (7)
Response at 3 mo					
No. of participants	359	—	360	184	360
Factor increase — % of participants (cumulative %)					
≥8.0×	86 (86)	—	60 (60)	89 (89)	1 (1)
4.0–7.9×	8 (94)	—	21 (81)	7 (96)	1 (2)
3.0–3.9×	2 (96)	—	5 (86)	2 (98)	1 (3)
2.5–2.9×	<1 (96)	—	3 (89)	1 (98)	1 (4)
2.0–2.4×	1 (97)	—	3 (92)	0 (98)	1 (6)
1.0–1.9×	1 (99)	—	4 (96)	1 (99)	7 (13)
Response at 12 mo					
No. of participants	374	—	371	185	377
Factor increase — % of participants (cumulative %)					
≥8.0×	24 (24)	—	57 (57)	58 (58)	2 (2)
4.0–7.9×	17 (41)	—	18 (76)	23 (81)	1 (3)
3.0–3.9×	9 (50)	—	7 (83)	6 (88)	1 (3)
2.5–2.9×	8 (57)	—	4 (87)	3 (91)	1 (4)
2.0–2.4×	4 (62)	—	3 (89)	3 (94)	2 (6)
1.0–1.9×	12 (74)	—	6 (95)	2 (95)	7 (13)
Children					
Response at 28 days					
No. of participants	389	580	391	189	369
Factor increase — % of participants (cumulative %)				—	
≥8.0×	50 (50)	80 (80)	—	—	1 (1)
4.0–7.9×	15 (66)	10 (90)	—	—	<1 (1)
3.0–3.9×	8 (74)	1 (91)	—	—	<1 (1)
2.5–2.9×	4 (77)	1 (92)	—	—	0 (1)
2.0–2.4×	6 (83)	1 (93)	—	—	1 (2)
1.0–1.9×	6 (89)	2 (95)	—	—	4 (6)

Table 4. (Continued.)

Variable	Ad26–MVA Group	Pooled rVSV Groups	rVSV Group	rVSV–Booster Group	Placebo Group
Response at 3 mo					
No. of participants	380	—	388	194	362
Factor increase — % of participants (cumulative %)					
≥8.0×	96 (96)	—	77 (77)	96 (96)	1 (1)
4.0–7.9×	2 (98)	—	13 (90)	3 (99)	<1 (1)
3.0–3.9×	1 (99)	—	2 (92)	0 (99)	1 (2)
2.5–2.9×	<1 (99)	—	1 (93)	1 (99)	1 (2)
2.0–2.4×	<1 (99)	—	1 (94)	0 (99)	0 (2)
1.0–1.9×	<1 (99)	—	1 (96)	1 (100)	6 (8)
Response at 12 mo					
No. of participants	381	—	385	189	364
Factor increase — % of participants (cumulative %)					
≥8.0×	61 (61)	—	75 (75)	80 (80)	1 (1)
4.0–7.9×	17 (78)	—	12 (87)	13 (93)	2 (4)
3.0–3.9×	7 (85)	—	4 (91)	3 (95)	1 (4)
2.5–2.9×	4 (89)	—	1 (92)	0 (95)	1 (5)
2.0–2.4×	2 (91)	—	1 (93)	1 (96)	1 (6)
1.0–1.9×	5 (96)	—	2 (95)	2 (97)	3 (9)

* Numbers of participants indicate participants who had a result at baseline and an antibody concentration of at least 200 EU per milliliter at the specified time point. Data for the rVSV group and the rVSV–booster group are pooled through day 28 because at that time point, participants in both groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine. Cumulative percentages (i.e., the percentages of all the participants with any factor increase ≥1.0) may not total as expected because of rounding.

Immune responses were elicited by 14 days after injection for these vaccine regimens and were maintained for 12 months. No safety concerns were identified, including in children as young as 1 year of age. Children had higher immune responses than adults.

APPENDIX

The affiliations of the members of the writing committee are as follows: the Partnership for Research on Ebola Virus in Liberia, Monrovia (M.K., S.B.K.); Unité 1219, Bordeaux Population Health, Inria, Statistics in System Biology and Translational Medicine (L.R., E.L.), Euclid–French Clinical Research Infrastructure Network Clinical Trials Platform (L.R., E.L., C.R., G.C.), University of Bordeaux,

INSERM, Institut Bergonié, Centre Hospitalier Universitaire de Bordeaux, Clinical Investigation Center–Clinical Epidemiology 1401, Bordeaux (L.R., E.L., C.R., G.C.), INSERM (E.D., R.V., H.E., A.D., A.W., Y.L., Y.Y.), ANRS Emerging Infectious Diseases (France Recherche Nord&Sud Sida-HIV Hépatites) (E.D., A.D., Y.Y.), and Assistance Publique–Hôpitaux de Paris, Hôpital Bichat–Claude Bernard, Service de Maladies Infectieuses et Tropicales (E.D., Y.Y.), Paris, and the Vaccine Research Institute, Université Paris-Est Créteil, Henri Mondor Hospital, Créteil (A.W., Y.L.) — all in France; Centre National de Formation et de Recherche en Santé Rurale de Maferinyah, Maferinyah, Guinea (A.H.B.); the Schools of Public Health (D.W., J.N.) and Statistics (B. Grund), University of Minnesota, Minneapolis; the College of Medicine and Allied Health Sciences, University of Sierra Leone, Freetown (B.L., M.S., G.F.D.); University Clinical Research Center, University of Sciences, Techniques, and Technologies of Bamako (S.D.), and Centre pour le Développement des Vaccins, Ministère de la Santé (M.D.), Bamako, Mali; the Center for Vaccine Development and Global Health, University of Maryland, Baltimore (S.S.), and the National Institute of Allergy and Infectious Diseases, Bethesda (J.P., B.D.-K., L.H., H.C.L.) — both in Maryland; Département de Sociologie, Faculté des Lettres et Sciences Humaines, Université Cheikh Anta Diop (S.F.), and the Alliance for International Medical Action (N.P.M., A.M.C.) — both in Dakar, Senegal; London School of Hygiene and Tropical Medicine, London (S.L., D.W.-J., P.P., B. Greenwood); Janssen Vaccines and Prevention, Leiden, the Netherlands (C.M.); and Merck Sharp and Dohme, Kenilworth, NJ (J.S.).

REFERENCES

1. Bartsch SM, Gorham K, Lee BY. The cost of an Ebola case. Pathog Glob Health 2015;109:4-9.
2. Emanuel J, Marzi A, Feldmann H. Filoviruses: ecology, molecular biology, and evolution. Adv Virus Res 2018;100:189-221.
3. World Health Organization. Ebola: N'Zerekore, Guinea, February–June 2021 (https://www.who.int/emergencies/situations/ebola-2021-nzerekore-guinea).
4. World Health Organization. Ebola: Équateur, Democratic Republic of the Congo, June–November 2020 (https://www.who.int/emergencies/situations/ebola-health-update---%C3%A9quateur-province-democratic-republic-of-the-congo-2020#:~:text=On%2018%20November%202020%2C%20the,Makanza%20Health%20Zone%2C%20Equateur%20Province).
5. European Medicines Agency. First vaccine to protect against Ebola. October 18, 2019 (https://www.ema.europa.eu/en/news/first-vaccine-protect-against-ebola).
6. Food and Drug Administration. First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. December 19, 2019 (https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health).
7. Merck. ERVEBO [Ebola Zaire vaccine (rVSVΔG-ZEBOV-GP) live] awarded prequalification status by the World Health Organization (WHO). November 13, 2019 (https://www.merck.com/news/ervebo-ebola-zaire-vaccine-rvsv%CE%B4g-zebov-gp-live-awarded-prequalification-status-by-the-world-health-organization-who/).
8. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet 2017;389:505-18.
9. Kennedy SB, Bolay F, Kieh M, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. N Engl J Med 2017;377:1438-47.
10. Gsell P-S, Camacho A, Kucharski AJ, et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. Lancet Infect Dis 2017;17:1276-84.
11. Anywaine Z, Whitworth H, Kaleebu P, et al. Safety and immunogenicity of a 2-dose heterologous vaccination regimen with Ad26.ZEBOV and MVA-BN-Filo Ebola vaccines: 12-month data from a phase 1 randomized clinical trial in Uganda and Tanzania. J Infect Dis 2019;220:46-56.
12. Mutua G, Anzala O, Luhn K, et al. Safety and immunogenicity of a 2-dose heterologous vaccine regimen with Ad26.ZEBOV and MVA-BN-Filo Ebola vaccines: 12-month data from a phase 1 randomized clinical trial in Nairobi, Kenya. J Infect Dis 2019;220:57-67.
13. Afolabi MO, Ishola D, Manno D, et al. Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in children in Sierra Leone: a randomised, double-blind, controlled trial. Lancet Infect Dis 2022;22:110-22.
14. Ishola D, Manno D, Afolabi MO, et al. Safety and long-term immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Sierra Leone: a combined open-label, non-randomised stage 1, and a randomised, double-blind, controlled stage 2 trial. Lancet Infect Dis 2022;22:97-109.
15. Barry H, Mutua G, Kibuuka H, et al. Safety and immunogenicity of 2-dose heterologous Ad26.ZEBOV, MVA-BN-Filo Ebola vaccination in healthy and HIV-infected adults: a randomised, placebo-controlled phase II clinical trial in Africa. PLoS Med 2021;18(10):e1003813.
16. World Health Organization. Weekly epidemiological record. Wkly Epidemiol Rec 2021;96:197-216.
17. Lévy Y, Lane C, Piot P, et al. Prevention of Ebola virus disease through vaccination: where we are in 2018. Lancet 2018;392:787-90.
18. Badio M, Lhomme E, Kieh M, et al. Partnership for Research on Ebola VACcination (PREVAC): protocol of a randomized, double-blind, placebo-controlled phase 2 clinical trial evaluating three vaccine strategies against Ebola in healthy volunteers in four West African countries. Trials 2021;22:86.
19. Grais RF, Kennedy SB, Mahon BE, et al. Estimation of the correlates of protection of the rVSVΔG-ZEBOV-GP Zaire ebolavirus vaccine: a post-hoc analysis of data from phase 2/3 clinical trials. Lancet Microbe 2021;2(2):e70-e78.
20. Pollard AJ, Launay O, Lelievre J-D, et al. Safety and immunogenicity of a two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis 2021;21:493-506.
21. Roozendaal R, Hendriks J, van Effelterre T, et al. Nonhuman primate to human immunobridging to infer the protective effect of an Ebola virus vaccine candidate. NPJ Vaccines 2020;5:112.
22. Heppner DG Jr, Kemp TL, Martin BK, et al. Safety and immunogenicity of the rVSVΔG-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. Lancet Infect Dis 2017;17:854-66.
23. Reinhardt B, Jaspert R, Niedrig M, Kostner C, L'age-Stehr J. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol 1998;56:159-67.
24. Agnandji ST, et al. Safety and immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccine in adults and children in Lambaréné, Gabon: A phase I randomised trial. PLoS Med 2016;14(10):e1002402.
25. Yoshida K, Cologne JB, Cordova K, et al. Aging-related changes in human T-cell repertoire over 20 years delineated by deep sequencing of peripheral T-cell receptors. Exp Gerontol 2017;96:29-37.
26. Bache BE, Grobusch MP, Agnandji ST. Safety, immunogenicity and risk-benefit analysis of rVSV-ΔG-ZEBOV-GP (V920) Ebola vaccine in phase I-III clinical trials across regions. Future Microbiol 2020;15:85-106.

Copyright © 2022 Massachusetts Medical Society.